

# Efficacy and tolerability of fixed dose combination of metoprolol and amlodipine in Indian patients with essential hypertension

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## ABSTRACT

**Background:** This open-labeled, post-marketing study was conducted to assess the efficacy and tolerability of fixed dose combination of amlodipine and metoprolol extended release capsules in mild to moderate hypertension in adult Indian patients.

**Materials and Methods:** Of 101 enrolled patients, 64 drug naïve patients were treated with regimen A (amlodipine 5 mg + metoprolol 25 mg) and those with prior history of hypertension ( $n = 37$ ) were treated with regimen B (amlodipine 5 mg + metoprolol 50 mg) for 8 weeks. Treatment response was assessed at week 4 and 8. Dose up titration to regimen B was carried out for those who failed to achieve the target blood pressure (BP) at week 4 in regimen A and additional antihypertensives were added to those in regimen B. Safety laboratory tests were performed at baseline and end of study.

**Results:** Mean age ( $\pm$ SD) of patients was 53.36 ( $\pm$ 11.26) years and body weight ( $\pm$ SD) 63.40 (10.03) kg. Ninety five patients (94.06%) were only hypertensive and 6 (5.94%) had hypertension with history of coronary artery disease; mean duration ( $\pm$ SD) of hypertension was 42.50 (48.07) months. At baseline, patients had a mean ( $\pm$ SD) systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 154.98 ( $\pm$ 7.76) mmHg and 95.55 ( $\pm$ 5.70) mmHg respectively. There was a statistically significant ( $P < 0.001$ ) reduction of 12.16% and 14.69% in SBP, 11.49% and 14.65% in DBP at week 4 and week 8 respectively, compared to baseline. Normalization of overall BP was achieved in 49.49% and 70.71% patients at week 4 and 8, respectively. Peripheral edema was reported in 2.97% (3/101) patients.

**Conclusion:** This combination was safe, efficacious, and well-tolerated in study population.

**Key Words:** Amlodipine and metoprolol, essential hypertension, fixed dose combination, peripheral edema

## INTRODUCTION

Hypertension, which is associated with mortality and long-term morbidity, is one of the biggest health challenges faced by mankind. It is one of the major risk factor for vascular disease world-wide<sup>[1]</sup> and also for cerebrovascular disease, ischemic heart disease, cardiac and renal failure. It has been projected that cardiovascular-related mortality in developed countries to increase from 5 million in 2000 to 6 million in 2020, and in under-developed and developing

countries from 10 million to 19 million,<sup>[2,3]</sup> affecting large proportion of working age population more so in developing countries.<sup>[4,5]</sup>

In recent times, many guidelines emphasize that the majority of the hypertensive population will require two or more antihypertensive drugs to achieve the recommended

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treatment goals.<sup>[1]</sup> Fixed drug combinations (FDCs) of antihypertensive agents have proven to be efficacious in the treatment of hypertension. With the availability of many antihypertensive agents in various classes of antihypertensives makes vast list such as diuretics, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$  adrenoceptor blockers are frequently combined in FDCs.

One of the advantages with the combination of a calcium channel blocker with a  $\beta$  adrenoceptor blocker is, their modes of action are different yet their action on blood pressure (BP) is complementary. The  $\beta$  adrenoceptor blocker might regulate any CCB-induced acute reflex increase in sympathetic activity and conversely, the CCB might compensate the peripheral vasospasm and drop in cardiac output caused by the  $\beta$  adrenoceptor blocker; thus, reducing the overall burden of side-effects. This is one key to ensure better long-term compliance with therapy and to more effective long-term BP control.<sup>[6]</sup>

Metoprolol, a selective  $\beta_1$  blocker is devoid of sympathomimetic activity and possess weak membrane stabilizing activity.<sup>[7]</sup> Controlled release/extended release (CR/ER) formulation of metoprolol succinate has been designed to provide relatively constant metoprolol plasma concentrations and  $\beta_1$  blockade, while retaining the convenience of once daily administration.<sup>[8]</sup> The avoidance of high peak plasma concentrations with metoprolol succinate is associated with lesser degree of adverse effects and may improve patient compliance.<sup>[9]</sup> Amlodipine is a dihydropyridine calcium channel blocker causing vasodilatation, reduction in peripheral vascular resistance, and hence, reduction in BP.<sup>[10]</sup> In combined analysis of clinical trials, amlodipine was found to have protection against stroke and myocardial infarction.<sup>[11]</sup>

This study was designed to assess efficacy, tolerability, and safety of fixed dose combination of amlodipine and metoprolol ER preparation in Indian hypertensive patients.

## MATERIALS AND METHODS

### Study design

This was a prospective, open label, multi-centric, phase IV clinical trial, conducted in five centers across India, in which 101 patients were enrolled. This study was conducted to document the real time experience of the FDC amlodipine and metoprolol in hypertensive patients. The treatment duration was 8 weeks with four visits including screening and the start of therapy was considered as week 0 followed by week 4, and week 8. The treatment responses were assessed at week 4 and week 8.

This study was conducted in accordance with good clinical practices and the Declaration of Helsinki as amended in Edinburgh, Scotland (October 2008). The protocol, statement of informed consent and other study documents were approved by regulatory authority of India, Institutional Ethics committee, prior to each center's initiation. Written informed consent was obtained from each patient prior to screening, in compliance with schedule Y.

The study was conducted between August 2009 and December 2009 and registered with the clinical trial registry of India (CTRI/2009/091/000269 [Registered on: 13/08/2009]).

### Patients

Adult patients aged  $\geq 18$  years and  $\leq 75$  years, with mild to moderate essential hypertension who are drug naïve or have not shown response to dietary and life-style modification or previous therapy (if different from study drug regimen) OR hypertensive patients with coronary artery disease (CAD)/CAD equivalents and provided a written informed consent were screened. The BP cut off for inclusion was,  $\geq 140/90$  mmHg and  $< 180/110$  mmHg. In isolated systolic hypertensive cases, cut off BP was SBP of  $\geq 140$  mm Hg. Response is taken as BP  $< 140/90$  mmHg at the time of assessment.

Those with history of intolerance or hypersensitivity reaction to any of the components in the combination, recent (within 6 months) myocardial infarction or stroke, hepatic dysfunction (aspartate amino transferase (AST)/alanine transferase (ALT)/alkaline phosphatase (AlkPO<sub>4</sub>) level more than 3 times upper limit of normal (ULN)/Bilirubin greater than 1.5 times ULN/known hepatic cirrhosis), Renal dysfunction (any of the renal function tests more than 3 times the ULN), Concurrent immunosuppressive or antineoplastic therapy, and drug or alcohol abuse were not screened. Those who received treatment with another investigational drug of less than 30 days prior to therapy, women of child bearing potential not practicing contraception, pregnant, and lactating women were excluded.

If the physician was of the opinion that changing a patient's medication would put the patient at risk (e.g., high-dose beta-blocker required to manage angina symptoms or for rate control in atrial fibrillation, accelerated/severe malignant hypertension, severe obstructive CAD, cardiac failure, uncontrolled diabetes mellitus, and severe renal insufficiency) were also excluded.

### Method

Patients who were willing to participate in the study and met the eligibility criteria were enrolled after screening.

The study medication was in two strengths, regimen A (FDC Amlodipine 5 mg + Metoprolol 25 mg ER) and regimen B (FDC Amlodipine 5 mg + Metoprolol 50 mg ER). Drug naïve patients received regimen A and regimen B was given to those whose BP was not controlled in spite of medication. Those who received regimen A, were up-titrated to regimen B at week 4, if they did not show therapeutic response. Patients who responded to treatment were continued on the same regimen. Investigators were advised to add additional antihypertensive agents at week 4 for the patients who received Regimen B and did not achieve the target therapeutic response. Patients were instructed to return the medicine container and remaining capsules were counted to measure the treatment compliance. Number of days since the previous visit during which the patient missed the dose was noted and recorded in the case report form (CRF) to check the compliance. Investigators were instructed to withdraw the patient who have not received treatment or if the treatment is delayed by more than 7 days during the trial period. Safety investigations were performed both at screening and end of the study. All adverse events (AEs), whether related or not were documented in the CRF. Investigators were instructed to report any serious adverse event (SAE) to the sponsor within 24 h of its occurrence.

### Statistical methods

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed primarily using the licensed version of Stata (release 10.0) for Windows. Statistical testing was performed at 0.05 level using two-tailed tests.

### Data analysis

The study population was considered for efficacy evaluation on modified intent to treat (mITT) basis. All patients having at least one post-baseline value were considered in mITT population. Last observation carried forward method was used to carry forward the missing entries as part of data imputation methods.

Evaluation of laboratory safety parameters was considered on intention to treat (ITT) basis. Adverse events were also analyzed based on ITT basis.

Descriptive analysis was used for demography.

The change in mean BP at week 4 and 8 versus baseline was analyzed using the paired test with 95% Confidence interval. Percentage of patients achieving normalization of BP was analyzed using descriptive analyses.

The number and percent of patients reporting adverse

events (AEs), grouped by the medical dictionary for regulatory activities [MedDRA] system organ class, and preferred term were tabulated. In the case of multiple occurrences of the same AE in the same patient, each patient was counted once for each preferred term. Treatment related events were also summarized.

Laboratory test results were summarized descriptively and analyzed using the paired *t*-test and McNemar's test was used for biochemical parameters to know the clinical relevance, if there was any statistically significant difference in the pre – and post-treatment.

Incidence of AEs (including SAEs) was summarized using frequency counts.

## RESULTS

Of 101 patients, the data of 99 patients were considered for efficacy analysis. One patient was lost to follow-up after enrollment and one patient's data was excluded due to major protocol violation. 96 patients completed the study [Figure 1].

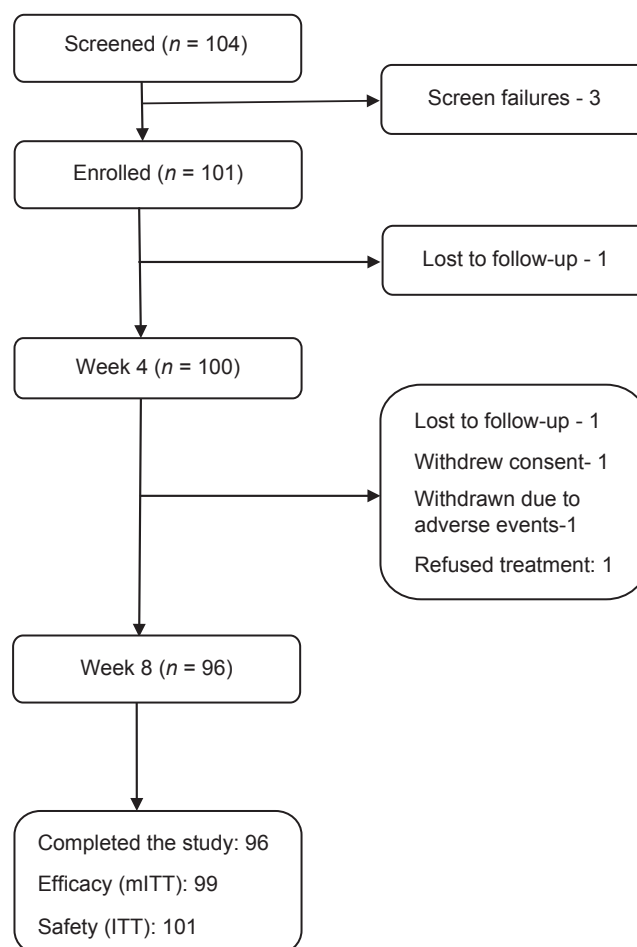


Figure 1: Study flowchart

A total of 52 (51.49) males and 49 females (48.51) with a mean age (+SD) of 53.36 (+11.26) years and body weight ( $\pm$ SD) 63.40 (10.03) kg were enrolled in to the study. Basic demographical characteristics are shown in Table 1. 95 (94.06%) were only hypertensives and six (5.94%) had hypertension with a history of CAD and with a mean duration ( $\pm$ SD) of hypertension of 42.50 (48.07) months. Patients had a mean ( $\pm$ SD) SBP of 154.98 ( $\pm$ 7.76) mmHg and maximum being 176 mmHg at baseline. Mean ( $\pm$ SD) diastolic blood pressure (DBP) of 95.55 ( $\pm$ 5.70) mmHg and maximum of 104 mmHg was observed at baseline.

Coexisting illness was seen in 54.45% patients, of which diabetes mellitus accounted for 29.70% [Table 2].

Anti-diabetic drugs were the most commonly prescribed concomitant therapy, followed by drugs for dyslipidemia and cerebrovascular accidents (CVA); few were receiving more than one concomitant therapy at baseline.

A total of 64 patients received regimen A and 37 patients received Regimen B as the initial treatment. Of these 64 patients in regimen A, 12 patients did not achieve adequate control with regimen A, and were up-titrated to regimen B. One patient dropped out of the study before week 4 and one patient refused to receive the medication further. In regimen B, four patients could not achieve adequate control and required additional anti-hypertensive drug (s) at 4<sup>th</sup> week [Table 3].

A total of 62 patients had normal body mass index (BMI) (BMI < 25), 30 were overweight (BMI = 25-<30) and 9 were obese (BMI30 and above).

Overall compliance was very good with all patients identified as taking the prescribed study medication with compliance greater than 90%.

### Efficacy analysis

#### Change in SBP

There was a significant reduction ( $P < 0.001$ ) in SBP at week 4 and week 8 compared to baseline. There was a significant reduction of 12.16% and 14.69% in SBP at week 4 and week 8 respectively, compared to baseline.

**Table 1: Demography**

Parameter	N	Mean	SD	Median	Minimum	Maximum	95% confidence interval	
							LCL	UCL
Age (year)	101	53.36	11.26	54.00	30.00	75.00	51.14	55.58
Height (cm)	101	160.23	7.70	160.00	143.00	179.00	158.71	161.75
Bodyweight (kg)	101	63.40	10.03	62.00	43.00	111.00	61.42	65.38

SD: Standard deviation; LCL: Lower confidence level; UCL: Upper confidence level

Of 99 patients, 58 (58.59%) patient's SBP became normal at week 4 and 76 (76.77%) had normal SBP at week 8.

#### Change in DBP

There was a statistically significant reduction ( $P < 0.001$ ) in DBP, 11.49% and 14.65% at week 4 and week 8 respectively, compared to baseline.

Of 99 patients who had high DBP at baseline, 61 (61.62%) had normal DBP at week 4 and 74 (74.75%) patients, at week 8.

#### Change in overall BP

Of 99 patients who had high BP at baseline 49 (49.49%) patients had normal BP at week 4 and 70 (70.71%) achieved normal BP at week 8.

There was a significant ( $P < 0.001$ ) difference in the normalization status of BP (SBP, DBP and overall BP) at week 8 compared to week 4.

**Table 2: Co-existing illness**

Co-existing illness	Frequency	
	n	%
Diabetes mellitus	30	29.70
Dyslipidemia	8	7.92
CVA	8	7.92
Hypothyroidism	3	2.97
Anxiety disorder	3	2.97
Obesity	2	1.98
Asthma	1	0.99
Total	55	54.45

CVA: Cerebrovascular accidents

**Table 3: Summary of study medication and dose titration**

Treatment	Frequency	%
Week 0		
Regimen A	64	63.37
Regimen B	37	36.63
Total	101	100
Week 4		
Regimen A	50	50.51
Regimen B*	49	49.49
Total	99	100

\*Four patients out of 49 in Regimen B, received additional drug

**Table 4: Dispersion of systolic and diastolic BP in study population at different visits**

Visits	No. of patient (N)	Mean	SD	Median	Min	Max	95% confidence interval	
							LCL	UCL
<b>Systolic BP</b>								
Baseline	99	154.98	7.76	154.00	140.00	176.00	153.44	156.53
Week 4	99	136.12	12.17	134.00	110.00	170.00	133.69	138.54
Week 8	99	132.20	8.36	130.00	110.00	160.00	130.53	133.86
<b>Diastolic BP</b>								
Baseline	99	95.55	5.70	98.00	70.00	104.00	94.41	96.63
Week 4	99	84.56	7.92	86.00	68.00	100.00	82.98	86.14
Week 8	99	81.56	5.70	80.00	66.00	98.00	80.08	83.04

BP: Blood pressure; LCL: Lower confidence level; UCL: Upper confidence level

Table 4 shows the dispersion of SBP and DBP during the treatment period and Table 5 denotes the changes in mean SBP and DBP with treatment.

At the end of the study, there was neither significant association between BMI and normalization of BP ( $P = 0.956$ ) on Chi-square analysis nor there was any significant contribution from BMI in the normalization of BP ( $P = 0.285$ ). There was no significant BMI cut-off that was predictive of normalization of BP with treatment ( $P = 0.490$ )

## Safety results

### Adverse events

There were six AEs reported in five patients. Peripheral edema 2.97% (3/101) was the most common AE, which was reported in three patients and was related to the study medication, probably to the amlodipine component. All these patients had hemoglobin (Hb) less than 12 g/dL at baseline (one patient had Hb of 11.6 g/dL at baseline, which was 12.1 at end of study and two had 11.7 g/dL which was 11.3 and 12.9 respectively at the end of study). Of these three, one patient had severe peripheral edema and was withdrawn from the study. The patient was followed-up and after a week time peripheral edema was resolved. Peripheral edema of mild and moderate degree was seen in one patient each. In these two patients, edema was resolved and improved respectively. Vertigo, lumbar spondylosis and eosinophilia (considered unlikely due to the study drug), were seen in one patient each and were mild in intensity. Though there were statistically significant changes in sodium, chloride, which showed decrease and blood urea, fasting blood sugar, which were increased, but these were clinically insignificant. Details of laboratory tests are shown in Table 6. The other AEs were of mild severity and not related to the study medication. Table 7 summarizes the AEs.

There was no SAE reported in the study.

**Table 5: Difference in systolic and diastolic BP with treatment**

Visit comparison	N	Difference between means	Simultaneous 95% confidence limits		Significance
<b>Systolic BP</b>					
Week 4-baseline	99	-18.86	-21.38	-16.35	***
Week 8-baseline	99	-22.78	-24.83	-20.73	***
Week 8-week 4	99	-3.91	-5.78	-2.05	***
<b>Diastolic BP</b>					
Week 4-baseline	99	-10.98	-12.85	-9.12	***
Week 8-baseline	99	-13.98	-15.78	-12.19	***
Week 8-week 4	99	-3.00	-4.35	-1.64	***

BP: Blood pressure; \*\*\*: Statistically significant

## DISCUSSION

Antihypertensive therapy aims at reducing the elevated BP, maintaining at normal range with minimal or no adverse effects without affecting quality of life. In long standing cases, maintaining BP at optimal target level, reducing associated mortality and morbidity becomes difficult with monotherapy, thus requiring the addition of one or more antihypertensive agents. The hypothesis that addition of different classes of anti-hypertensive agents may potentiate antihypertensive actions of these drugs there by aiming at better BP control, led to the development of FDC in the management of hypertension. It is also assumed that FDCs enhance tolerability, treatment compliance and may minimize adverse effects by their antagonizing action. In addition, they may also exert and enhance protective effects on target organs thereby minimizing complications that arise from hypertension.<sup>[12]</sup> FDCs have been found to be cost-effective also.<sup>[13]</sup> It has been observed that 75% patients require combination therapy to achieve target BP.<sup>[14,15]</sup> Combination of amlodipine and metoprolol was found to be therapeutically effective in patients with mild to moderate hypertension<sup>[16]</sup> than amlodipine and losartan.<sup>[17]</sup> Response rate with combination of amlodipine and metoprolol was higher than those with individual agents.<sup>[16,18]</sup>

**Table 6: Summary of laboratory parameters**

Parameter	Baseline mean $\pm$ SD	EOS mean $\pm$ SD	P value
Aspartate amino transferase	24.01 $\pm$ 14.24	21.63 $\pm$ 7.80	0.119
Alanine transaminase	24.46 $\pm$ 15.23	22.82 $\pm$ 14.26	0.134
Alkaline phosphatase	110.31 $\pm$ 56.15	113.94 $\pm$ 55.99	0.390
Bilirubin	0.55 $\pm$ 0.22	0.93 $\pm$ 0.2	0.264
Random blood sugar	128.57 $\pm$ 42.39	134.45 $\pm$ 53.67	0.481
Sodium	140.44 $\pm$ 3.28	138.94 $\pm$ 3.52	0.000*
Potassium	4.31 $\pm$ 0.49	4.24 $\pm$ 0.45	0.261
Chloride	103.79 $\pm$ 4.85	102.46 $\pm$ 4.46	0.008*
Uric Acid	5.13 $\pm$ 1.24	4.95 $\pm$ 1.11	0.162
Urea	23.10 $\pm$ 6.74	24.60 $\pm$ 7.52	0.027*
Creatinine	0.93 $\pm$ 0.25	0.95 $\pm$ 0.22	0.389
Creatine kinase	128.57 $\pm$ 94.47	123.74 $\pm$ 57.99	0.317
Red blood cells	4.56 $\pm$ 0.59	4.57 $\pm$ 0.60	0.801
White blood cells	7852.00 $\pm$ 2045.32	7788.91 $\pm$ 2169.121	0.757
Platelet	279.58 $\pm$ 67.58	285.02 $\pm$ 79.71	0.398
Hemoglobin	12.94 $\pm$ 1.99	12.85 $\pm$ 1.75	0.269

\*Statistically significant. AST: Aspartate amino transferase; ALT: Aspartate amino transferase; AlkPO<sub>4</sub>: Alkaline phosphatase; EOS: End of study

**Table 7: Description of AEs**

Description	No. of events
Intensity	
Mild	4
Moderate	1
Severe	1
Not related	3
Causality	
Probable	0
Possible	0
Definite	3
Unknown	0
Action taken	
None	2
Remedial drug therapy	3
Study drug discontinued	1
Outcome	
Resolved	3
Improved	2
Insufficient follow-up	1

AEs: Adverse event

Combination of amlodipine and metoprolol has been efficacious and well-tolerated in Indian population<sup>[16]</sup> and results of our study confirm this. Baseline BP of our study population was similar to the study population studied by Devi *et al.*,<sup>[16]</sup> where baseline mean BP ( $\pm$ SD) was 154.87  $\pm$  11.91/96.63  $\pm$  6.97 mmHg indicating that our patients were under standard risk. Similar observations were noted by Patel *et al.*,<sup>[18]</sup> Too in Indian patients.<sup>[18]</sup>

In our study, after 8 weeks treatment, amlodipine and metoprolol FDC significantly reduced systolic and DBP in mild to moderate hypertensive patients. Similar observation was seen in previous study by Devi *et al.*, too.<sup>[16]</sup> We observed a mean reduction of 22.88 mmHg in SBP and 13.98 mmHg in DBP. The drug was effective in normalizing SBP in 76.77% of patients after 8 weeks therapy. DBP was normalized in 74.75% of patients. The normalization of BP was achieved in 70.71% of the patients. The results of the study are similar to the earlier studies carried out on FDC of CCB and beta-blocker.<sup>[17,19]</sup>

In our study, BMI was not predictive of normalization of BP, did not contribute to normalization status and did not have any association with normalization pattern. This could have been due to smaller sample size of the study.

The FDC was well-tolerated by the study population. The most common AE was peripheral edema, which is an expected AE seen with amlodipine therapy.<sup>[10]</sup> There were three (2.9%) cases of peripheral edema, and one patient (<1%) was withdrawn from the study because of the same. These findings are similar to the published clinical trial literature, where the incidence of edema with 5 mg amlodipine was 3% and 1.5% patients were excluded due to adverse reactions.<sup>[10]</sup> However, Patel *et al.* Have reported higher incidence of peripheral edema (12%) in Indian population; they have also reported headache (12%), fatigue (10%) and dizziness (6%) as other AEs.<sup>[18]</sup> In our study, On subanalysis, we observed that all these patients who reported peripheral edema had hemoglobin of < 12 g/dL and were females.

Earlier studies have shown that the combination of metoprolol and amlodipine is safe and there are no reported SAEs in these studies.<sup>[16,18]</sup> Our study confirms this as there was no reported SAE in our study indicating that the tested combination treatment is safe and well-tolerated.

In actual clinical setting, one of the reasons for not achieving hypertension control is patients failing to adhere to treatment regimen. Many patients who are on multi-drug therapy have low adherence as they tend to be more irregular with their daily intake of medications. The FDCs decrease the non-adherence.<sup>[20]</sup> The compliance with this FDC was above 90% in our study, which is another factor in favor of study medication as long-term drug compliance is expected to have a positive effect on cardiovascular and renal outcome.<sup>[21]</sup> Since the FDCs have shown to be efficacious, safe with good tolerability, to improve the treatment compliance and cost-effectiveness, this combination can be used in the management of hypertension.

Though the earlier studies have not shown significant reductions in BP compared to individual components of this FDC, better response rate with early control of BP, better treatment compliance has been observed with this combination. This open label study without any comparator, supports this finding. However, we recommend long-term comparative studies to verify its effects on target organs and also in larger population.

## CONCLUSION

This multi-centric clinical study demonstrated the efficacy of the FDC of amlodipine and metoprolol ER capsules in essential hypertension. Since the FDCs have shown to be efficacious, safe with good tolerability, improve the treatment compliance and are cost-effective. This combination of amlodipine and metoprolol can be used in the management of mild to moderate hypertension.

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